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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,801	03/25/2008	**Germain Puzo**	0512-1404	6107

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	

NOTIFICATION DATE	DELIVERY MODE
05/27/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/553,801	PUZO ET AL.	
	Examiner	Art Unit	
	GANAPATHY KRISHNAN	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-47* is/are pending in the application.

4a) Of the above claim(s) *44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-43 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a preliminary amendment on 03 July 2007 in which claims 1-23 had been cancelled and Claims 24-47 were presented for prosecution on the merits.

Restriction/Election

Applicant's election with traverse of Group I in the reply filed on 28 February 2011 is acknowledged. The traversal is on the ground(s) that Groups II-IV are directed to a method of using compounds of Group I which constitutes a single general inventive concept on the basis that Vergne et al does not disclose sulfoglycolipids of formula (I) of the invention.

This is not found persuasive because Vergne teaches trehalose comprising 2'sulfate group and his compound has fatty acyl substitution at the 3-position as instantly claimed. Trehalose having 2'-sulfate and fatty acyl substitutions are known in the art. The instant invention therefore, does not define a contribution over the prior art. The instant compound does not have a methoxyl group (-OCH_3) at the 5' position as stated by applicants. The 5'-position in the instant compound is a hydroxymethyl group (-CH_2OH). The requirement is still deemed proper and is therefore made FINAL.

Applicants have stated in their Remarks that they elect Group I, claims 20-40 and 47. Group I as presented in the Election/Restriction mailed 21 January 2011, had claims 24-40 and 47.

After review of the Election/Restriction the Examiner has decided to rejoin Groups II-IV, claims 41, 42 and 43 with Group I, claim 24-40 and 47.

Therefore, Claims 24-43 and 47 are pending in the instant application and are examined on the merits herein.

This application contains claims 44-46 drawn to an invention nonelected with traverse in the reply filed on 28 February 2011.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

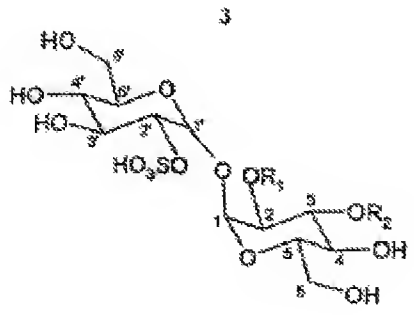
Claim Objections

Claim 38 is objected to because of the following informalities: In claim 38 the notation BCG should be expanded. Appropriate correction is required.

Specification

The amendment filed 03 July 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

In the Specification as originally filed on 18 October 2005, at page 2, line 25 discloses that the present invention relates to compounds of general formula I



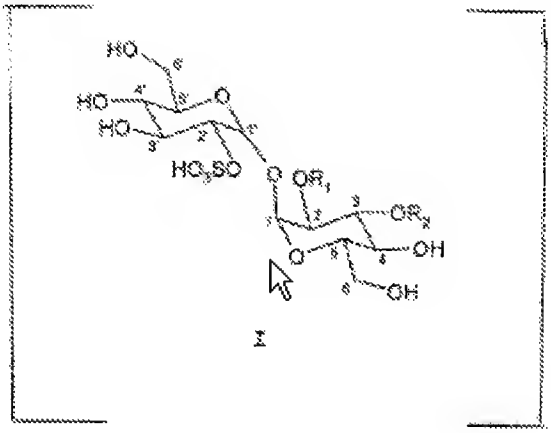
I

wherein R_1 and R_2 are fatty acyl groups.

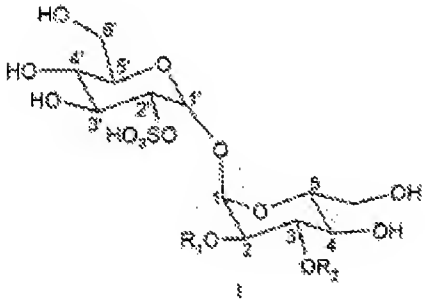
But in the preliminary amendment filed 03 **July** 2007 the following structures have been inserted as replacements in the specification:

Please replace the paragraph beginning at page 2, line 24, with the following rewritten paragraph:

--The invention relates to compounds of the following general formula (I):



I



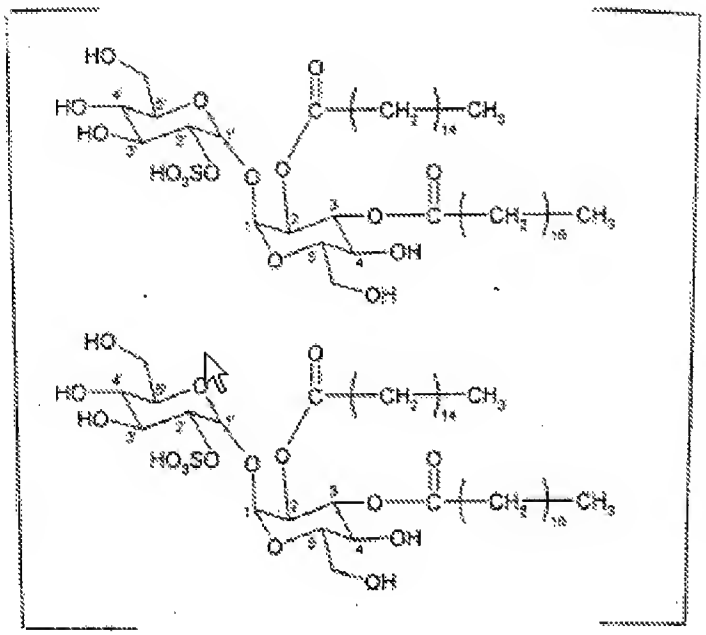
I

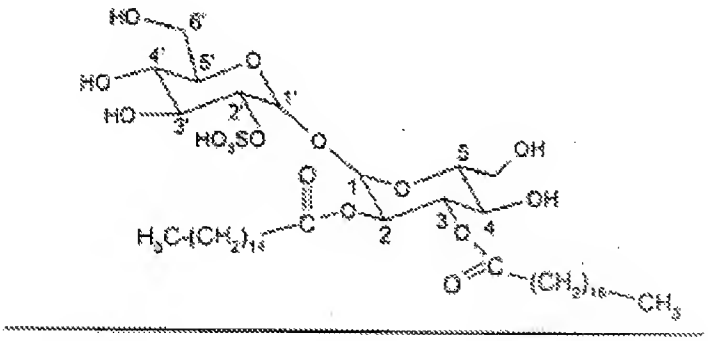
wherein R_1 and R_2 are fatty acyl groups.--

Please replace the paragraph beginning at page 4, line 3, with the following rewritten paragraph:

-- The invention more particularly relates to compounds of formula I, wherein R_1 and R_2 are selected from the group

comprising palmitic acyl and stearic acyl, namely compounds of following formulae:





and several other structural formulas as shown above. The preliminary amendment filed 03 July 2007 containing the structures above are different from the compounds of formula I as originally filed on 18 October 2005. The disclosure in the preliminary amendment filed 03 July 2007 constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 24-43 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to compounds of instant formulae I-III which are substituted disaccharides (substituted Trehaloses).

The MPEP states that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. See MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618. Additionally, in *Carnegie Mellon University v. Hoffman-La Roche Inc.*, Nos. 07-1266, -1267 (Fed. Cir. Sept. 8, 2008), the Federal Circuit affirmed that a claim to a genus described in

functional terms was not supported by the specification's disclosure of species that were not representative of the entire genus. Furthermore, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The claims are rejected under the written description requirement for failing to disclose any species for the claimed genus, the genus being the fatty acyl substituted disaccharide trehalose.

The Guidelines for Examination of Patent Applications under the 35 USC § 112, first paragraph, "Written Description" Requirement", published at Federal Register, Vol. 66, No. 4, pp. 1099-1111 outline the method of analysis of claims to determine whether adequate written description is present. The first step is to determine what the claim as a whole covers, i.e., discussion of the full scope of the claim. Second, the application should be fully reviewed to understand how applicant provides support for the claimed invention including each element and/or step, i.e., compare the scope of the claim with the scope of the description. Third, determine whether the applicant was in possession of the claimed invention as a whole at the time of filing. This should include the following considerations: (1) actual reduction to practice, (2) disclosure of drawings or structural chemical formulas, (3) sufficient relevant identifying characteristics such as complete structure, partial structure, physical and/or chemical properties and functional characteristics when coupled with a known or disclosed correlation between

function and structure, (4) method of making the claimed invention, (5) level of skill and knowledge in the art and (6) predictability of the art. For claims 24-43 and 47, each of these factors have been considered, with the most relevant factors discussed below. For each claim drawn to a genus, each of these factors is to be considered to determine whether there is disclosure of a representative number of species that would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. Where skill and knowledge in the art is high, adequate written description would require fewer species to be disclosed than in an art where little is known; further, more species would need to be disclosed to provide adequate written description for a highly variable genus.

First, what do the claims as a whole cover? Claims 24-39 are draw to compounds of formula I-III, their compositions and methods of use.

Second, how does the scope of the claims compare to the scope of the disclosure? The compounds claimed is different in scope than what is supported in the disclosure as originally filed. The claims are drawn to compounds having a sulfo and fatty acyl substituted disaccharides of formulas I-III, but the disclosure as originally filed provides compounds of formula I-III (at page 3-9 of the specification originally filed) which are different structurally compared to compounds of formula I-III are recited in claims 24-39.

Third, the factors need to be considered, with the most relevant factors discussed below.

Reduction to Practice: The compounds reduced to practice are those disclosed in Table 1 at page 17 of the specification. Again, these are different compared to the ones claimed.

Disclosure of Drawings or Structural Chemical Formulas: The only disclosures seen are compounds in Table 1 at page 17 of the specification which has the sulfo disaccharide labeled A

(page 16) having palmitic, stearic and hydroxythioceranoic groups attached to the sulfo disaccharide A. This is not seen to constitute a written description of every species in the genus as claimed, because it would not "reasonably lead" those skilled in the art to any other particular species. Therefore, there is no disclosure of species (e.g. by disclosure of structural/chemical formulae) in addition to the above, which have been reduced to practice.

Level of Skill in the Art and Knowledge in the Art: The level of skill in the art is a person with experience in organic synthesis.

Thus, having analyzed the claims with regard to the Written Description guidelines, it is clear that the specification does not disclose a representative number of species for the structures claimed. Thus, one skilled in the art would be lead to conclude that Applicants were not in possession of the claimed invention at the time the application was filed.

Claims 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of tuberculosis, does not reasonably provide enablement for the prophylaxis of tuberculosis as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention

The invention is drawn to pharmaceutical compositions comprising fatty acyl substituted sulfo trehaloses and other products useful for prophylaxis of tuberculosis.

The state of the prior art

According to The Merck Manual (pages 141-142) chemoprophylaxis is indicated for tuberculosis only in subjects where tuberculin skin test is positive. This means that the subject has been infected and then treatment is done.

The breadth of the claims

The instant claims recite the term "Prophylaxis". Applicants have not provided the definition for the said terms. In the absence of a definition of the said term the ordinary dictionary meaning is used. “Preventing” or “Prophylaxis" as recited in the instant claims, based on the ordinary dictionary meaning (Dictionary.com) is to keep from happening or existing. The term prophylaxis is also seen to encompass absolute prevention of the said infections. In the

instant case both the terms recited mean keeping the said tuberculosis infections from happening in a mammal and is interpreted to mean the complete and total blocking of all symptoms of the recited infections for an indefinite period. "Prophylaxis" as recited in the instant claims, is interpreted to mean the complete and total blocking of all symptoms of a disease/disorder (tuberculosis in the instant case) for an indefinite period of time. Prophylaxis is seen to include the administration of the said compounds to a healthy mammal, and subsequent exposure to conditions that would cause tuberculosis, wherein the said compounds prevent said exposure from manifesting itself in said mammal so exposed. Any therapy which merely reduces the number or severity of symptoms, or which is effective for a period shorter than the subject's remaining lifespan, is considered to be ineffective at preventing a disease/disorder. In general, preventing diseases/disorders linked to an outside stimulus or insult according to the definition of prophylaxis given above is not possible as any so-called prophylactic effects of a drug therapy are expected to cease when the drug is cleared from the patient's system. More generally, prophylaxis of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The predictability or unpredictability of the art

According to Merck Manual (above) prophylaxis of tuberculosis is highly unpredictable. Treatment is suggested only after infection is confirmed via tests for infection in a subject. The art is silent regarding prevention of tuberculosis.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the

prophylaxis of tuberculosis as instantly claimed. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for using the instant method with regard to prophylaxis.

The presence or absence of working examples

Example 3, at pages 19-20 shows an ex vivo assay of the effect of sulfoglycolipid antigens on the viral strain of M. tuberculosis. This shows the effect of the glycolipids on the bacterial strain. This example is not an enabling disclosure for the prophylaxis of tuberculosis as instantly claimed.

The quantity of experimentation necessary

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the prophylaxis of tuberculosis via administration of the claimed active agents to an infected subject. One of ordinary skill in the art would have to carry out the method inorder to test if there is a prophylactic effect.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the use of the claimed method.

Genetech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors as discussed above, e.g., the amount of guidance provided and the predictability of the art, to practice the claimed invention herein, a person of

ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-43 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is drawn to a compound of formula I and further recites limitations regarding substitutions R_1 and R_2 being fatty acyl groups. Instant formula I (the formula underscored) does not show substitutions R_1 and R_2. It is not clear what is claimed.

Claims 25-35 recites the limitation "a compound" in claim 24. There is insufficient antecedent basis for this limitation in the claim.

Regarding claims 32 and 38, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claim 32 also recites two different compounds of formula I whereas a single compound of formula I is recited in parent claim 24. This also applies to claims 33-43 and 47.

Claims 38 and 39 recite, 'other product(s)'. The specification (at page 10) recites some examples of other products useful for treating tuberculosis. The instant recitation is broad and is seen to include several compounds. Thus, it is not possible to interpret and ascertain the metes

and bounds of the patent protection desired regarding the active agents present in the claimed composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Desmarais et al (J. Bacteriology, 1997, 3146-53).

Desmarais et al teach the sulfated disaccharide, 1-(2-O-sulfo-alpha-D-glucopyranosyl)-alpha-D-glucopyranose (abstract; limitation of claim 24). Desmarais teaches a composition of this disaccharide with other sugars and glutamate in water (page 3147, left column, see under subtitle; Purification of disaccharide; limitation of claims 36-39). Water is a pharmaceutically acceptable vehicle as recited in claim 36. The composition in water is in the form for oral administration. The other sugars and glutamate constitute the other product in the composition as recited in claims 38 and 39. The use of these other products as recited in claims 38-39 is intended use and is not given patentable weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-37 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vergne et al (Frontiers in Bioscience, 1998, 3, 865-76; document cited in IDS) in view of Besra et al (Biochemistry, 1992, 31, 9832-37).

Vergne et al teach 2'-sulfated trehalose acyl derivatives (page 866, Fig. 1B) with fatty acyl substitutions having C16 and C18 chains at the 2 and 3-positions as recited in instant claims 26-34 (page 866, section 3.1.2.). These trehalose derivatives which are obtained form M.tuberculosis (page 867, Table 1) are antigenic in tuberculosis (page 870, Table 2). This means

that administration of these compounds to a patient infected by the tuberculosis bacteria should produce an immune response (limitations of claims 40-43). Vergne et al do not teach the compound of formula I in claim 24, the compounds with substitutions other than palmitic acyl and stearic acyl as recited in claims 25-35.

Besra et al, drawn to acyltrehaloses from M.tuberculosis, that the acyl trehaloses from M. tuberculosis are antigenic (page 9832, right col., lines 8-9). The compounds have a range of fatty acyl groups represented by structures I-III (page 9835, Fig. 5). These are the types of substitutions recited in instant claims 24-35. One of the compounds identified is shown in Fig. 8 (page 9836). This is trehalose with substitutions in the 2 and 3-positions that are fatty acyl groups. The only difference is that there is no sulfo substitution in the 2-position of the sugar ring at the top. But one of ordinary skill in the art in view of this and Vergne's teaching would have a reasonable expectation of success regarding the use of the compounds as instantly claimed, i.e., trehalose having a sulfo group and fatty acyl substitutions at the 2 and 3 positions also to be antigenic in tuberculosis. Hence the skilled artisan would look for such compounds in M. Tuberculosis and also use these compounds in the methods of treatment as instantly claimed.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look for the compounds as instantly claimed and use them in a method of treatment as instantly claimed since structurally analogous compounds having the substitutions recited in the instant claims are known in the art to be antigenic to tuberculosis. It is well within the skill level fo the artisan to make compositions comprising more than one active agent in a wide range of percentages as recited in instant claims 32-35. Such compositions would have the additive effect of the individual active agents.

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ,82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

According to the rationale discussed in KSR above, the rationale in (A)-(C) above are seen to be applicable here since based on the prior art teachings, both a trehalose with only a 2-sulfo group and a trehalose having only acyl substitutions at the 2 and 3 positions of the sugar

ring are both known in the art and are also known to be antigenic in tuberculosis. Thus, it is obvious to combine prior art elements and improve the product and method of the prior art to yield predictable results by looking for trehalose derivatives having the sulfo at the 2'-position and fatty acyl substitutions at the 2- and 3- positions of the sugar rings and use them as an active agent in a pharmaceutical composition and in a method of treatments as instantly claimed. Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art. Product/method improvement is the motivation.

Claims 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vergne et al (Frontiers in Bioscience, 1998, 3, 865-76; document cited in IDS) in view of Besra et al (Biochemistry, 1992, 31, 9832-37) and further in view of The Merck Manual (1992, pages 140-41).

The teachings of Vergen and Besra are as set forth in the obviousness rejection above. However, they do not expressly teach a composition comprising fatty acyl substituted sulfo trehalose and another product as instantly claimed. However both Vergne and Besra do not expressly teach a composition comprising the fatty acyl sulfo trehalose and another product as instantly recited.

The Merck Manual teaches that bacilli Calmette-Guerin (BCG) is a a vaccine used in the treatment of tuberculosis (page 141, third full paragraph; limitations of claims 38-39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising fatty acyl substituted sulfo trehaloses as instantly

claimed and other products like BCG since BCG is known for treating tuberculosis and the trehalose derivatives are known to be antigenic in tuberculosis (see Vergne and Besra).

MPEP 2141 states, "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusatory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ,82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) " Obvious to try " choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

According to the rationale discussed in KSR above, the rationale in (A) and (C) above are seen to be applicable here since based on the prior art teachings, both a trehalose with only a 2-sulfo group and a trehalose having only acyl substitutions at the 2 and 3 positions of the sugar ring are both known in the art and are also known to be antigenic in tuberculosis. BCG is useful for treating tuberculosis. Thus, it is obvious to combine prior art elements and improve the product of the prior art to yield predictable results by making a pharmaceutical composition comprising the fatty acyl substituted sulfo trehaloses and BCG. Such a composition would have the additive effect of both the active agents against tuberculosis.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art. Product improvement is the motivation.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Besra et al (Biochemistry, 1992, 31, 9832-37).

Besra et al teach the isolation of fatty acyl substituted trehaloses (similar to the one instantly claimed) wherein the sulfoglycolipids are extracted from Mycobacterium tuberculosis using chloroform, methanol and water to obtain an extract with the polar components in the organic phase (; page 9832, see under Experimental Procedure; step 1 in instant claim). Besra further teaches that some additional components were detected using chloroform, methanol, water and acetone (the solvent recited in step 3 of the instant claim) as the solvent mixture via chromatography on silica gel.

Even though Besra does not expressly teach the steps of adding acetone and performing chromatography of the concentrate over silica as recited in steps 3-6 of the instant claim, one of

ordinary skill in the art will recognize that the use of acetone results in additional components from the initial chloroform-methanol-water extract. Hence the artisan would take the chloroform methanol extract and concentrate the chloroform phase and add acetone to it to extract any acetone soluble components into it and perform chromatography of the acetone phase to look for additional components.

It would have been obvious to one of ordinary skill in the art at the time the invention made to use the extraction with acetone as an additional step in the extractive process taught by Besra et al since its use in detection of extra components in thin layer chromatography is taught by Besra. One of ordinary skill in the art also knows well that that separation by chromatography is due also in part because of difference in solubility of a component in the solvent used. Since the use of acetone ($(CH_3)_2C=O$) as a solvent is taught by Besra the artisan would be motivated to look for additional components and separate as many new components in the original extract by further adding acetone to the chloroform concentrate and getting an acetone phase and looking for additional components in it after separation by chromatography of the acetone phase. Such will be recognized and is also well within the skill level of the artisan.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-43 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31, 37-38, 40, 42-46 and 48 of copending Application No. 12/524,091 ('091). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant claims are drawn to 2'-sulfo fatty acyl substituted trehalose derivatives, their pharmaceutical compositions and methods of treatment of tuberculosis and activation of immune reaction.

The claims of the copending '091 also recite derivatives of 2'-sulfo acyl substituted trehalose derivatives that overlap, pharmaceutical compositions and the method of treatment of tuberculosis using the claimed compounds.

The claims of '091 differ from the instant claims in that they also include compounds that have substitutions that are not encompassed by the instant claims. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that trehalose derivatives instantly claimed could be used in the composition and method of treatment recited in '091.

In the instant case '091 teaches the compounds, compositions and method of treatment applicant claims. Although the claims of '091 employ other substitutions that are different, one

of ordinary skill in the art would readily recognize that the compounds compositions and methods taught by '091 could be employed in the instant case with a reasonable expectation of success. The use of known members of classes of active agents, their compositions and their methods of use taught in the prior art is not seen to render the instantly claimed compounds, compositions and methods of use unobvious over the art. Once the compounds and the methods of use have been shown to be old, the burden is on the applicant to present reason or authority for believing the non-obviousness of the instant compounds and the methods of their use.

With respect to the non-statutory double patenting rejection(s) made in this Office action, note as follows. The use of the terminology "defined in 35 U.S.C. §154 to §156 and §173" in a terminal disclaimer can result in the terminal disclaimer being found improper. To address this, note that a proper terminal disclaimer need only disclaim the patent's remaining "full statutory term" as defined in 35 U.S.C., without specifying 35 U.S.C. 154 and 173. This is so, because the "full statutory term" inherently is a statutorily defined item.

Accordingly, the following language would be deemed acceptable:

The owner*, _____, of _____ percent interest in the instant application hereby disclaims,
except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond
the expiration date of the full statutory term of any patent granted on pending **reference** Application Number _____, filed
on _____, and as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in

whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Note: the above language corresponds to PTO/SB/25 (07-09) (reproduced at page 1400-120 in Revision 7 (July 2008) of the 8th edition of the MPEP), but the reference to 35 U.S.C. 154 and 173 has been deleted.

Conclusion

Claims 24-43 and 47 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GANAPATHY KRISHNAN whose telephone number is (571)272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/
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